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EXAMINER	
PARKIN, J	
ART UNIT	PAPER NUMBER
1648	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

Office Action Summary

Application No.	Applicant(s)
09/146,783	Deacon et al.
Examiner	**Group Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

X Responsive to communication(s) filed on *30 Aug 2000*.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-119* is/are pending in the application.

Of the above, claim(s) *1-48, 68-84, and 86-119* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *49-67 and 85* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Detailed Office Action

Status of the Claims

1. Applicant's election with traverse of Group III, claims 49-67 and 85, in Paper No. 9 is acknowledged. The traversal is based upon the argument that the inventions of Groups I-XIII, which are set forth in 119 claims, are not independent and distinct. Applicants further maintain that the inventions are interdependent, that the classification system is unreliable, that the restriction requirement places and undue financial burden on the applicants, and that subsequently filed divisional applications may be vulnerable to legal challenge.

Applicants are reminded that the regulations governing restriction requirements are set forth in 37 C.F.R. § 1.141 and 1.142. Two criteria currently exist for the determination of proper restriction requirements (see M.P.E.P. § 803): 1) The inventions must be independent (see M.P.E.P. § 802.01, 806.04, and 808.01) **or** distinct as claimed (see M.P.E.P. § 806.05); and 2) There must be a serious burden on the examiner if restriction is not required (see M.P.E.P. § 803.02, 806.04(a)-(j), 808.01(a), and 808.02).

Establishment of *prima facie* evidence for a serious burden requires the demonstration, by appropriate explanation, of either separate classification, separate status in the art, or a different field of search as defined in M.P.E.P. § 808.02. The following items adduce a *prima facie* showing of burden: 1) The inventions of Groups I-XIII display both separate classifications and a separate status in the art as set forth in the last Office action (see Paper No. 7). The following independent and distinct groups were identified in said Office action:

a. Group I, claims 1-29, drawn to a **non-pathogenic HIV-1 strain**, classified in class 435, subclass 236.

b. Group II, claims 30-48 and 85, drawn to a **method of inhibiting HIV-1 infection** by administering a therapeutic composition comprising a non-pathogenic HIV-1 isolate, classified in class 424, subclass 208.1.

c. Group III, claims 49-67 and 85, drawn to a **method of vaccinating subjects** with a therapeutic composition comprising a non-pathogenic HIV-1 isolate, classified in class 424, subclass 208.1.

d. Group IV, claims 68-79, drawn to a **method for the preparation** of non-pathogenic HIV-1 isolates from biological samples, classified in class 435, subclass 237.

e. Group V, claims 80-82, drawn to a **screening method** for the identification of putative antiviral compounds employing a *nef* fusion protein, classified in class 435, subclass 7.1.

f. Group VI, claims 83-84, drawn to a **compound** capable of inhibiting nef gene activity, classified in class 424, subclass 278.1.

g. Group VII, claim 86, drawn to a **therapeutic composition** comprising a non-pathogenic HIV-1 isolate that is also capable of expressing a **ribozyme or antisense molecule**, classified in class 536, subclass 24.5.

h. Group VIII, claims 87-93, drawn to a **non-pathogenic viral isolate** comprising a modified genome capable of expressing an **antisense or ribozymal molecule** that inhibits HIV-1 replication, classified in class 424, subclass 93.2.

i. Group IX, claims 94-110 and 115, drawn to a **method for determining the pathogenicity** of an HIV-1 strain through the detection of **deletion mutations** in the viral genome, classified in class 435, subclass 91.2.

j. Group X, claims 111-114 and 116, drawn to a **method for determining the pathogenicity** of an HIV-1 strain by employing a **peptide-based assay**, classified in class 435, subclass 34.

k. Group XI, claims 117, drawn to a **peptide** comprising SEQ ID NO.: 801 or a fragment thereof, classified in class 530, subclass 326.

l. Group XII, claims 118, drawn to **antibodies** that bind to a peptide comprising SEQ ID NO.: 801 or a fragment thereof, classified in class 530, subclass 387.1.

m. Group XIII, claim(s) , drawn to a **method of risk assessment** employing a peptide defined by SEQ ID NO.: 801, classified in class 436, subclass 506.

2) The inventions of Groups I-XIII are directed towards different inventive concepts. Accordingly, each invention will generate unique issues regarding novelty, patentability, and enablement. Reasoning explaining the basis for these differences was also set forth in the last Office action (see Paper No. 7) wherein the following explanations were provided:

> Inventions I, VI-VIII, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects (refer to M.P.E.P. ¶s 806.04 and 808.01). In the instant case each of the aforecited inventions is directed toward a different product (e.g., non-pathogenic HIV-1 isolate, antiviral compound, therapeutic composition, modified non-pathogenic HIV-1 isolate expressing an antisense molecule, peptide, and antibody) with different structures and functions. Accordingly, each invention is clearly drawn toward a different inventive concept.
>
> Inventions II-V, IX, X, and XIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects (refer to M.P.E.P. ¶s 806.04 and 808.01). In the instant case each of the aforecited inventions is directed toward a different methodology that employs different scientific reagents and methodology steps, and is directed toward a different scientific objective (e.g., methods of inhibiting viral infection, methods of vaccinating subjects, antiviral screening methods, methods for assessing viral pathogenicity, and methods of risk assessment). Accordingly, each invention is clearly drawn toward a different inventive entity.
>
> Inventions I/VI-VIII/XI/XII and II-V/IX/X/XIII are unrelated except where noted in subsequent paragraphs seven through nine. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects (refer to M.P.E.P. ¶s 806.04 and 808.01). In the instant case, none of the products are required to practice the methodologies and the methodologies do not require any of the identified products in order to be performed. Therefore, each invention is clearly drawn toward a different inventive concept.
>
> Inventions I and II/III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. ¶ 806.05(h)). In the instant case, the non-pathogenic HIV-1 isolate can be employed in a number of different methodologies such as antiviral screening assays, the generation of immunological reagents, and as a

diagnostic reagent in diagnostic assays. Moreover, the cited methodologies can employ materially different products such as subunit vaccines or known antivirals.

Inventions XI and XIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. ¶ 806.05(h)). In the instant case the peptide of Group XI can be employed in materially different processes such as the generation of immunological reagents or affinity purification protocols. Moreover, the method can employ materially different products such as PCR primers for the detection of non-pathogenic HIV-1 isolates.

Inventions I and IV are related as product made and process of making. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process as claimed can be used to make other and materially different products, or (2) the product as claimed can be made by another and materially different process (M.P.E.P. ¶ 806.05(f)). In the instant case the non-pathogenic isolate can be made through a materially different process such as PCR amplification. Moreover, the process claimed can be employed to make materially different products such as pathogenic HIV-1 isolates.

3) Since the inventions disclosed *supra* are directed towards patentably distinct material, a search for one invention would not necessarily result in the identification of art that is concomitant with that required to address the issues generated by the other inventions. Therefore, **the original restriction requirement is still deemed to be proper and is therefore made FINAL.** Claims 1-48, 68-84, and 86-119 are withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Claims 49-67 and 85 will be examined on the merits.

35 U.S.C. § 112, Second Paragraph

2. Claim 85 is rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim references a non-elected claim.

Applicants are reminded of the restriction requirement set forth *supra* and in the last Office action. The claim should be amended to reflect the requirement and election (i.e., A vaccine composition comprising a non-pathogenic HIV-1 isolate ...).

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 65 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. It is apparent that the non-pathogenic HIV-1 isolates having the designations V94101706, V941031169, and V95031022 are required to practice the claimed methodology. However, the specification does not appear to provide a repeatable method for obtaining non-pathogenic HIV-1 isolates with the precise genotypic and phenotypic characteristics of these isolates. Moreover, these isolates do not appear to be readily available materials. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the claimed strains. See 37 C.F.R. § 1.802.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her

signature, stating that the deposit has been made under the terms of the Budapest Treaty **and** that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

Applicants may obviate the rejection by depositing the claimed isolates under the provisions of the Budapest Treaty. If a deposit is made under these terms, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposits will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposits will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification. See 37 C.F.R. § 1.803-1.809 for additional explanation of these requirements.

5. Claims 49-67 and 85 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broadly directed toward vaccine compositions and methods of vaccination employing non-pathogenic HIV-1 isolates. The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The specification does not provide any guidance pertaining to the selection of mutations, truncations, or decanucleotide deletions in the HIV-1 viral genome that will produce viruses of the desired non-pathogenic phenotype. The specification defines non-pathogenic at the clinical level as a strain that does not produce the clinical sequelae associated with AIDS within the median time of 6-10 years post infection. At the laboratory level non-pathogenic strains do not produce changes in $CD3^+$, $CD4^+$, and $CD8^+$ cell counts or induce p24 antigenaemia. However, the disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating the pathogenic properties of any given virus. The specification fails to teach which genotypic changes in the viral genome (i.e., LTR, *gag*, *pol*, *env*, *vif*, *vpr*, *tat*, *rev*, *vpu*, *nef*) will produce a non-pathogenic isolate. Absent

such guidance an undue invitation to further experimentation has been extended to the skilled artisan.

2) The prior art teaches that many viral and host factors contribute to the pathogenicity of any given isolate. However, deciphering the molecular viral and cellular determinants contributing to this process has been quite problematic and the disclosure fails to provide any illumination concerning this topic. The problem of addressing this question was addressed by Kirchhoff *et al.* (1995), who PCR-amplified the *nef* coding region from HIV-1-infected long term nonprogressors. Although the authors identified a single patient with reproducible deletions in *nef*, the authors emphasized that these results should be interpreted with considerable caution:

> In this report, we describe a particular HIV-1 gene defect associated with the absence of disease progression in a single patient. Our results, and those of Huang *et al.*,[17] suggest that **deletions in *nef* may not be a common explanation for the absence of progression and that different factors are likely to contribute in other patients. Viral factors that could contribute include different types of mutations in a wide variety of viral genetic elements.** Viral and host factors cannot be dissociated from each other, since an effective immune response is an essential feature of nonprogression. Disease outcome is likely to be determined by a delicate balance between the ability of the virus to replicate and the host's ability to mount an adequate immune response. [Emphasis added by Examiner].

Huang *et al.* (1995) also performed PCR analysis on proviral DNAs obtained from long-term survivors of HIV infection. The authors reported that:

> We found that there is no gross deletion within *nef* in the cases studied; most *nef* sequences (91.1%) obtained from 10 subjects contained a full-length and intact open reading frame. In addition, **at the protein level, there were no discernible differences between the Nef consensus sequences derived from long-term survivors and those from patients with AIDS.** We therefore conclude that deletion of or gross sequence abnormality within *nef* is not likely to be a common

explanation for the well-being of long-term survivors of HIV-1 infection. [Emphasis added by Examiner].

Additional studies by Michael *et al.* (1995) corroborated these findings. It was reported by this group that:

> We have studied the sequence and function of the human immunodeficiency virus type 1 (HIV-1) *nef* genes from nine patients with highly divergent rates of disease progression enrolled in a longitudinal study of HIV disease ... The *nef* gene from each of these patients was amplified and cloned, and the sequence of 8 to 10 clones was determined. Only 2 of 88 (2.3%) *nef* genes recovered from these nine patients were grossly defective. Moreover, **there was no relationship between the phylogeny of *nef* sequences and the corresponding rates of disease progression from these patients ... There was no correlation found between the functions of the *nef* genes from these patients and their corresponding rates of disease progression.** We conclude that the *nef* gene is not a common mediator of the rate of HIV disease progression in natural infection.

The prior art clearly illustrates that other viral, as well as, cellular gene products contribute to the pathogenic phenotype. Moreover, the specification asserts that changes in *nef* may contribute to disease progression, nevertheless, it is not readily manifest if each of the identified clones has been completely characterized at the molecular level and the contributions of other viral gene products and regulatory regions examined. For instance, the LTNP phenotype may result from a modification in Tat or TAR that results in lower levels of viral replication. Considering the unpredictability of the prior art, it would be premature to conclude that Nef is responsible for the LTNP phenotype, absent complete characterization of the various clones. Moreover, the findings of the prior art would preclude the skilled artisan from extending the findings of the instant application to any other HIV-1 isolate, particularly since it appears that all the clones described in the specification evolved from the same progenitor.

3) The specification fails to disclose which components, parts,

fragments, or derivatives thereof, contain the molecular determinants governing pathogenicity. In order for the skilled artisan to practice the instantly claimed invention and generate HIV-1 isolates with attenuated pathogenicities, the molecular determinants governing these properties need to be ascertained. However, the specification does not provide any guidance and the prior art teaches that these determinants remain to be elucidated.

4) The specification fails to provide adequate guidance concerning the selection of allelic variants of *nef*, or any other HIV viral gene, that contain the requisite phenotypic properties. Terwilliger *et al.* (1991) observed that allelic variants of *nef* provide different contributions to the replicative properties of HIV-1. The authors reported the following:

> The effects of the viral gene *nef* on human immunodeficiency virus type 1 (HIV-1) replication in culture were investigated using *nef* alleles of the HIV-1 IIIB and ELI strains. The results demonstrate significant allelic variation in the effect of *nef* on virus replication in both an established human $CD4^+$ T-cell line and primary human lymphocytes. In the context of HXB2 virus, the ELI *nef* allele but not the IIIB *nef* allele permits initiation of efficient low-multiplicity infection in primary peripheral blood mononuclear cells, including unfractionated peripheral blood lymphocytes, T cells, and monocyte/macrophages. Within the same genetic context, **the IIIB *nef* allele slightly retards replication of the virus in a T-cell line, whereas the ELI *nef* allele accelerates replication of the virus.** Sequences in the IIIB and ELI genomes outside of *nef* also moderate the effects of *nef* on HIV-1 replication. [Emphasis added by Examiner].

In view of the teachings of the prior art, how could the skilled artisan reasonably predict which *nef* allelic variants will produce the desired LTNP phenotype?

5) The specification fails to clearly set forth those criteria that the skilled artisan should employ to ascertain the pathogenic properties of any given variant. What constitutes a non-pathogenic virus? If a clinical definition is employed, how are these

characteristics to be ascertained? If a laboratory definition is employed, which precise biochemical properties must an HIV-1 variant contain to be considered non-pathogenic?

6) The specification fails to demonstrate that the instantly claimed HIV-1 vaccines or therapeutics employing *nef*⁻ deletion variants would mount an efficacious humoral or cellular immune response resulting in the prevention or treatment of HIV infection and the clinical sequelae leading to AIDS. There are a number of attendant caveats associated with the development of an efficacious HIV-1 vaccine and these were reviewed by Graham *et al.* (1995) and Haynes (1993). The rational design of an effective vaccine requires a knowledge of the pathogenesis of HIV infection and an understanding of the human correlates of protective immunity. The cruxes associated with vaccine development can be summarized as follows: 1) The correlates of human protection remain to be elucidated. Thus, it is not clear if humoral, cell-mediated, or both types of immune response will provide protection.

2) The plasticity, or quasispecies nature, of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of an effective vaccine. Convincing data demonstrating that such a vaccine can neutralize diverse field isolates remains to be presented.

3) The most appropriate methods for presenting viral antigens to the immune system remains to be elucidated. Thus, it is not readily manifest which mechanisms will optimize MHC Class I- or II-dependent antigen uptake, processing, compartmentalization, and presentation.

4) The viral antigens that confer protective immunity are poorly understood. Thus, the skilled artisan cannot predict which immunogens (i.e., Gag, Pol, Env) should be included in a putative vaccine and the form they should take (i.e., whole viral vaccine, sub-unit).

5) The viral and cellular determinants responsible for mucosal immunity remain to be elucidated. This route of administration plays a major role in viral transmission. Any efficacious vaccine will need to generate a strong mucosal immune response, probably through the production of neutralizing secretory IgA antibodies, to prevent the mucosal transmission of HIV-1.

6) Adequate animal models are not available for vaccine efficacy testing. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies can not be directly extrapolated to a clinical setting. Graham *et al.* (1995) specifically note (refer to pp. 1333-1334) that the "structural differences between SIV and HIV complicate the direct translation to humans of the results of vaccine studies in the SIV-macaque system" and that "no animal model has been found in which an AIDS-like illness develops from a virus with the antigenic determinants of HIV-1." It was further emphasized by Haynes (1993; refer to p. 1280) that "In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection."

7) The prior art raises a number of additional concerns pertaining to the development of an AIDS vaccine specifically involving *nef*-deficient viruses were raised by Ruprecht *et al.* (1995). The findings of this article can be summarized as follows: 1) SIV mutants containing *nef*, *vpr*, and negative regulatory element (NRE) deletions replicated to high levels following oral administration to infant macaques. All of the animals receiving this "vaccine" either developed SAIDS or display symptoms of the disease (Baba *et al.*, 1995). 2) The *nef* gene product is not a direct molecular determinant for virulence. Nef appears to modulate the viral load while other determinants are responsible for the direct pathogenic properties of the virus. Accordingly, *nef*-deficient viruses are

replication-impaired, not avirulent, and can be activated (thereby becoming virulent) by additional host, bacterial, or viral factors. 3) Protective immune responses to SIV *nef* mutants developed quite slowly following administration of the putative vaccine. A dilatory immune response in humans could facilitate spread of the disease through high risk behavior by encouraging a false sense of protection. 4) Replication-impaired retroviruses still undergo integration into the host chromosome. This activity can potentially result in insertional mutagenesis. Disseminated lymphoproliferative disorders were associated with the administration of an SIV *nef* "vaccine". The authors soundly conclude (refer to page 178, final paragraph) that "We feel that it is premature to consider *nef*-deleted viruses as candidate AIDS vaccines; they are neither safe nor sufficiently effective. The race between vaccine-virus replication and host defenses could be decided in favour of virus replication in coinfected or immunocompromised hosts." Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

6. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

7. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

8. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

17 November, 2000